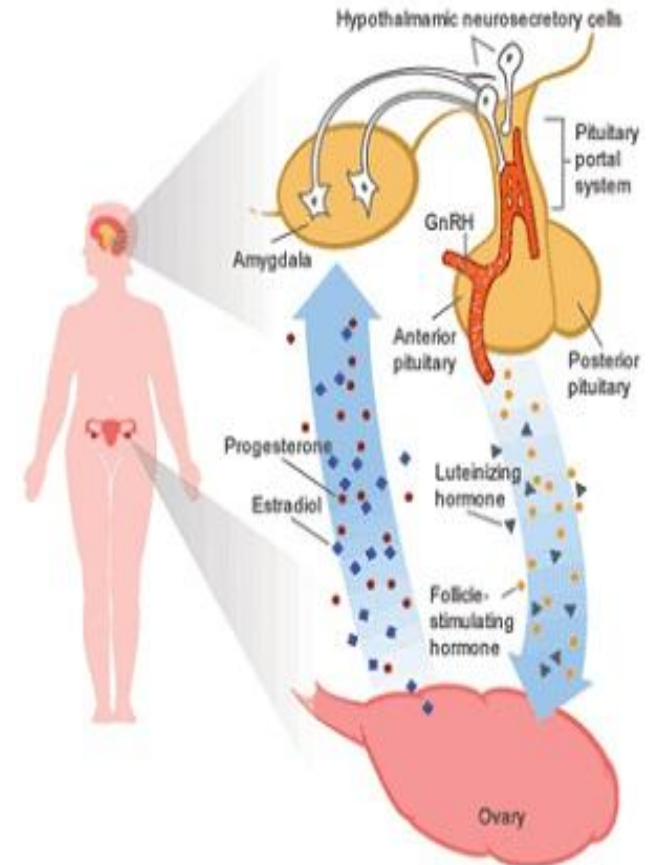


Hormonal Replacement Therapy (HRT)

Lecture-4-
Reproductive Block
Ahlam Sultan

Overview

- **Sex hormones** produced by the gonads are necessary for conception, embryonic maturation, and development of primary and secondary sexual characteristics at puberty
- The gonadal hormones are used therapeutically in:
 - ✓ Replacement therapy
 - ✓ Contraception
 - ✓ Management of menopausal symptoms



Menopause

- Menopause is a naturally occurring events and part of the normal life cycle of women
- Occurs for most women between their **mid-40 and mid-50**, it may start **early as late-30**
- It is the permanent end of spontaneous menstruation caused by **cessation of ovarian function**



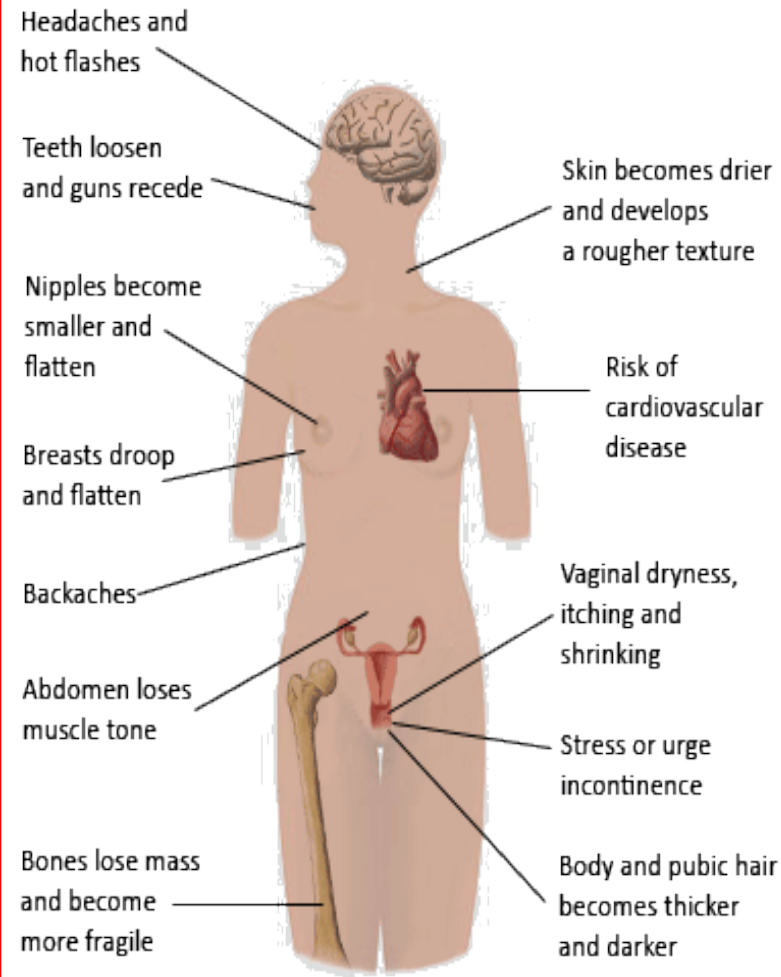
Menopause

Decrease production of estrogen at menopause results in symptoms Like:

- **Hot flushes**
- **Sweating**
- Vaginitis
- Anxiety and fatigue
- Urogenital atrophy
- Muscles and joints pain
- **Osteoporosis**
- **Skin Dryness**
- Increase risk of cardiovascular disease
- Psychological disturbances



Menopause Symptoms



Hormone Replacement Therapy (HRT)

- One of the most complex health care decisions facing women is whether to use postmenopausal HRT or not

(Definitive Answer is Challenging)

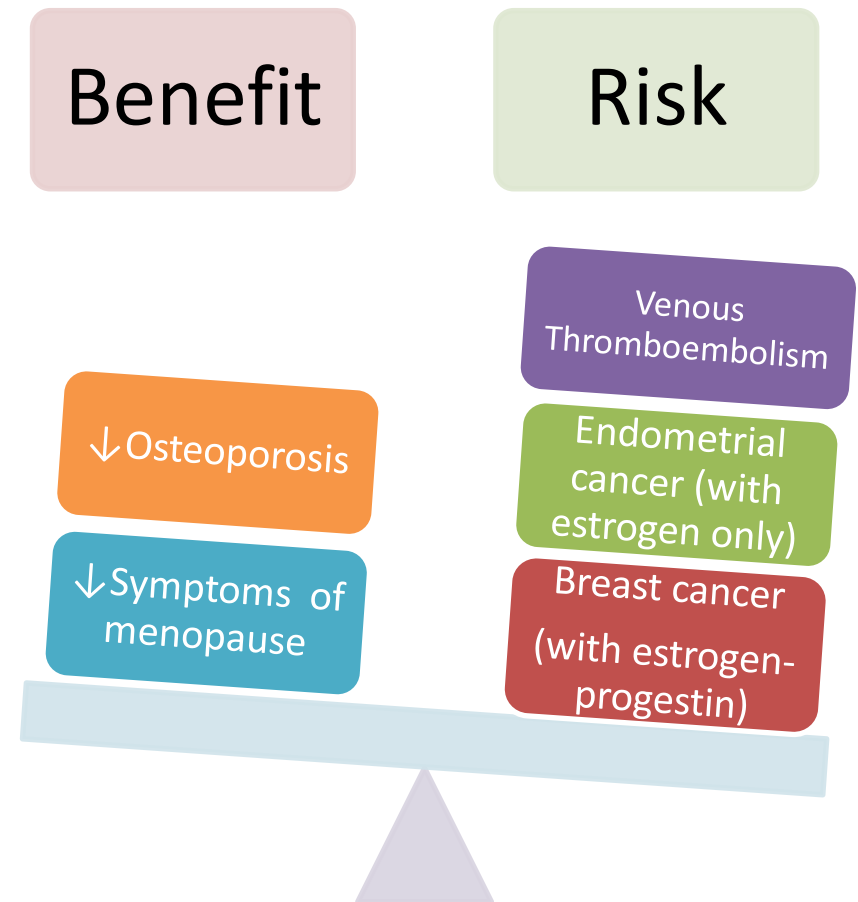


Hormone Replacement Therapy (HRT)

- The first clinical usage of hormone replacement therapy (HRT) in the setting of **menopause** began in the 1950s, with the administered estrogen purified from the **urine of pregnant mare**
- From that time until 1975, estrogen was administered without supplemental progesterone or progestin
- A study demonstrated that in the absence of progesterone, patients were at increased risk of **endometrial cancer** with unopposed estrogen therapy
- **HRT relief of symptoms related to menopause most commonly:** hot flushing and vaginal dryness
- This was followed by the **Women's Health Initiative (WHI) in 2002**

Hormone Replacement Therapy (HRT)

- HRT was used for the treatment of menopause until 2002 when the **women health initiative (WHI) results were published**
- WHI examines more than 27,000 postmenopausal women age 50-79 (mean age, 63) for an average of 5-7 years, **was stopped early** because of an overall unfavorable risk-benefit ratio in estrogen-progestin arm and an excess risk of stroke in estrogen only arm
- Prevention of CVD is eliminated from the equation due to lack of evidence for such benefit



Benefits and risks of HRT

Definite benefits

1- Symptoms of menopause:

- Estrogen therapy is highly effective for controlling vasomotor and genitourinary symptoms
- For genitourinary symptoms, the efficacy of vaginal estrogen is similar to that of oral or transdermal estrogen

2- Reduce risk of Osteoporosis:

- By reducing bone turnover and resorption rate
- Estrogen therapy rapidly increases bone mineral density
- lower risk of fracture



Benefits and risks of HRT

Definite Risk

1- Endometrial cancer (estrogen alone):

- User of unopposed estrogen has increase risk for endometrium cancer development
- Use of a progesterone, which opposes the effects of estrogen on the endometrium, eliminate this risk

2- Venous thromboembolism:

- Estrogen-progestin therapy and estrogen alone therapy show similar result they increase risk for venous thromboembolism



Benefits and risks of HRT

Definite Risk

3- Breast cancer (with estrogen-progestine)

- An increased risk of breast cancer has been found among HRT users

4- Gallbladder disease:

- HRT increase risk of:
 - ✓ Gallstones, or
 - ✓ Cholecystectomy



Benefits and risks of HRT

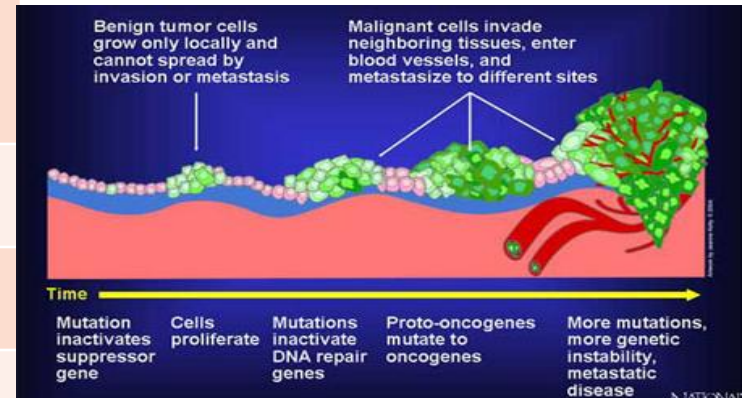
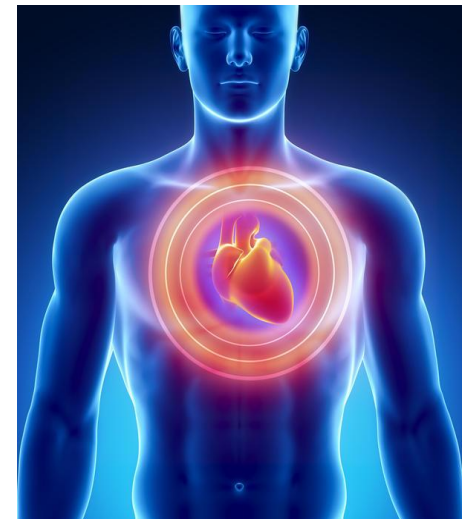
Probable or uncertain Risks and Benefits

Probable increase in risk

- 1- Coronary heart diseases
- 2- Stroke
- 3- Ovarian cancer

Benefit (Probable decrease)

- 1- Colorectal cancer
- 2- Diabetes Mellitus
- 3- Dementia



Hormone Replacement Therapy (HRT)

- In WHI cohort study:
 - ✓ the risk disappeared within 2.4 years after discontinuation of therapy, as did the benefit
 - ✓ A slight elevation for breast cancer persisted
- ***When should we use HRT??***

We need to balance potential risks and benefits
- HRT has become one of the most **controversial topics** related to women's health



CHART TO IDENTIFY CANDIDATES FOR HT^a

1. Significant symptoms of menopause (moderate to severe hot flashes, night sweats)?^b

No

Yes

No HT

2. Contraindications to HT?^c

No

Yes

No HT^g

3. Assess CHD risk and years since final menstrual period

	Years since final menstrual period ^e		
	≤5	6–10	>10
Very low (<5%)	Go to Q4	Go to Q4	No HT
Low (5 to <10%)	Go to Q4	Go to Q4 ^f	No HT
Moderate (10 to <20%)	Go to Q4 ^f	No HT	No HT
High (≥20%)	No HT	No HT	No HT

CHD risk over 10 years
(Framingham
CHD risk score)^d

4. Increased risk of stroke (e.g., Framingham Stroke Risk Score of ≥10% over a 10-year period)?

No

Yes

No HT

5. Select duration of HT use^h based on type of therapy and breast cancer risk

	Estrogen plus progestogen		Estrogen alone	
	<5 years	≥5 years	<7 years	≥7 years ⁱ
Below average or average	HT OK	Uncertain; go to Q6 ^k	HT OK	Uncertain; go to Q6
Above average	Avoid HT ^l	No HT ^m	Avoid HT ^l	No HT ^m

Breast Cancer Riskⁱ

6. Only if response to Q5 above is "uncertain," then consider:

At increased risk of osteoporotic fracture?ⁿ

If no, convert "uncertain" in Q5 to "No HT."

If yes, convert "uncertain" in Q5 to "HT OK."

Hormone Replacement Therapy (HRT)

HRT includes:

- ✓ **Estrogen-Progestin therapy** for used with women who have intact uterus
- ✓ **Estrogen therapy** for use with women who have had a hysterectomy, sole therapy with estrogen is contraindicated if the uterus is still present due its proliferative effect on the endometrium
- It is the estrogen component in HRT that **relieves the symptoms of menopause**
- The progesterone, is the major anabolic hormone for breast tissue, is added to **protect the uterine endometrium** from hyperplasia and endometrial cancer

Hormone Replacement Therapy (HRT)

HRT is available in:

- **Oral** preparation
- **Transdermal** application
- **Vaginal** preparation (contain estrogen only): creams, suppositories, pellets, or ring

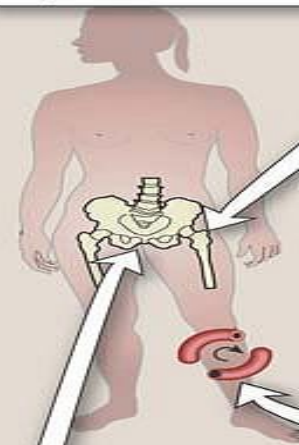


Hormone Replacement Therapy (HRT)

- Due to recent concerns over the risks of HRT, the National American Menopause Society recommends that HRT be prescribed at the **lowest effective dose** for the **shortest possible time** to relieve vasomotor symptoms and vaginal atrophy
- Women that have only urogenital symptoms should be treated with vaginal rather than systemic estrogen
- *Younger women with **surgical menopause** or **premature ovarian failure** may use HRT for many years, until the age that natural menopause would be expected to occur*

OSTEOPOROSIS

- Estrogen decreases the resorption of bone but has no effect on bone formation.
- Estrogen decreases the frequency of hip fracture. [Note: Dietary calcium (1200 mg daily) and weight-bearing exercise also slow loss of bone.]
- Treatment with estrogens must begin within 2 or 3 years of menopause —and earlier if possible.



VASOMOTOR

- Estrogen treatment reestablishes feedback on hypothalamic control of norepinephrine secretion, leading to decreased frequency of "hot flashes."

UROGENITAL TRACT

- Estrogen treatment reverses postmenopausal atrophy of the vulva, vagina, urethra, and trigone of the bladder.

Hormone Replacement Therapy (HRT)

HRT are contraindicated in:

- ✓ History of **endometrium cancer**
- ✓ History of **breast cancer**
- ✓ History of **thromboembolic disorders**
- ✓ Acute and chronic **liver disease**
- ✓ History of **CHD**
- ✓ History of **stroke**
- ✓ **Diabetes**
- ✓ **Undiagnosed vaginal bleeding**



Hormone Replacement Therapy (HRT)

Relative contraindications:

- Hypertriglyceridemia
- Atypical ductal hyperplasia of the breast
- Active gallbladder disease (cholangitis, cholecystitis)

[Note: Primary prevention of heart diseases should not be viewed as an expected benefit of HRT]

Hormone Replacement Therapy (HRT)

“Cyclic HRT” or “sequentially combined HRT”:

- Dosage is often varied cyclically to more closely mimic the ovarian hormone cycle
- Estrogens taken daily and progesterone or progestins taken for about 2 weeks every month or two

“Continuous combined HRT”:

- A constant dosage with both types of hormones taken daily

Estrogen

Estrogen product:

- **Natural conjugated estrogen**, e.g., **Premarin** (*obtained from pregnant mare's urine*)
- **Synthetic estrogen**, e.g., **Ethinyl estradiol** and **mestranol** (*undergo less first-pass metabolism than naturally occurring steroids, effective when administered orally*)

Estrogen

- Bioavailability of *estrogen taken orally is low due to first-pass metabolism in the liver*. To reduce first-pass metabolism, the drugs may be administered by:

☐ Transdermal patch

☐ Topical gel

☐ Emulsion

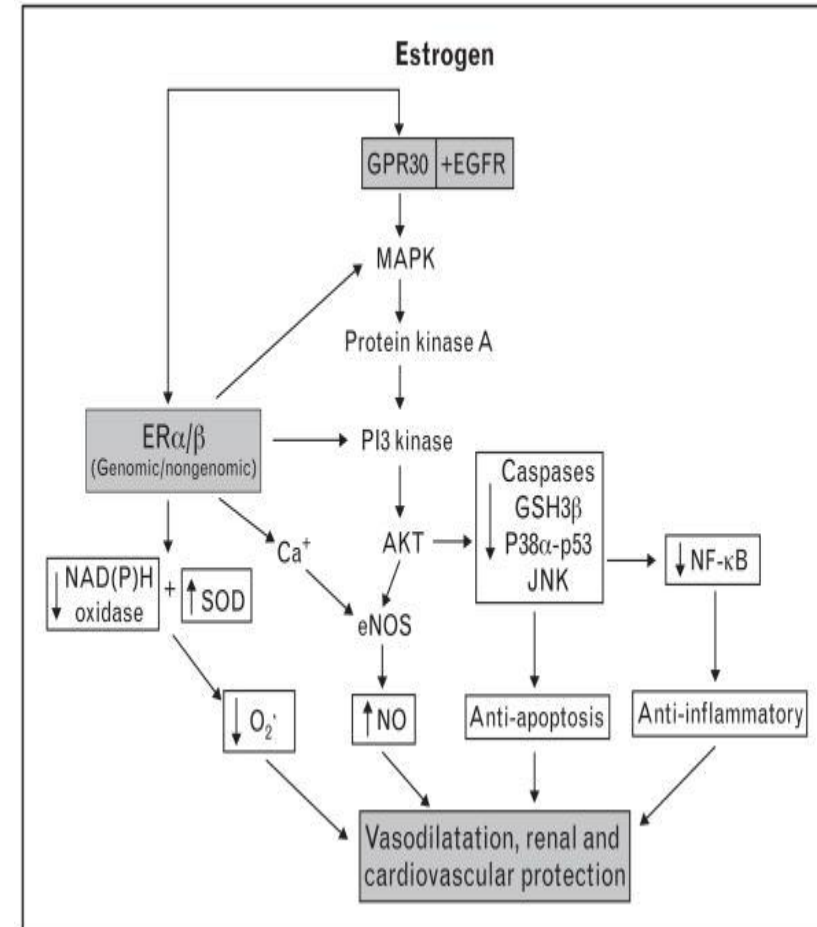
☐ Intravaginally

☐ Injection

[Note: Estrogen is metabolized in the liver In individuals with liver damage, serum estrogen levels may increase due to reduced metabolism]

Mechanism of action of Estrogen

- Bind to specific intracellular **estrogen receptors [ER- α and ER- β]**
- The hormone receptor complex interact with specific DNA sequences and alters the transcription rates of target genes
- Lead to change in the synthesis of specific proteins within targeted cells
- In addition, estrogen **mediate dilation of coronary arteries** occurs by increase formation of nitric oxide and prostacyclin in endothelial cells



Effects of Estrogen

Brain

Estrogen helps to maintain body temperature.

Estrogen may delay memory loss.

Estrogen helps to regulate parts of the brain that prepare the body for sexual and reproductive development.

Heart & Liver

Estrogen helps to regulate the liver's production of cholesterol, thus decreasing the build-up of plaque in the coronary arteries.

Ovary

Estrogen stimulates the maturation of the ovaries.

Estrogen stimulates the start of a woman's menstrual cycle – an indication that a girl's reproductive system has matured.

Vagina

Estrogen stimulates the maturation of the vagina.

Estrogen helps maintain a lubricated and thick vaginal lining.

Breast

Estrogen stimulates the development of the breasts at puberty and prepares the glands for future milk production.

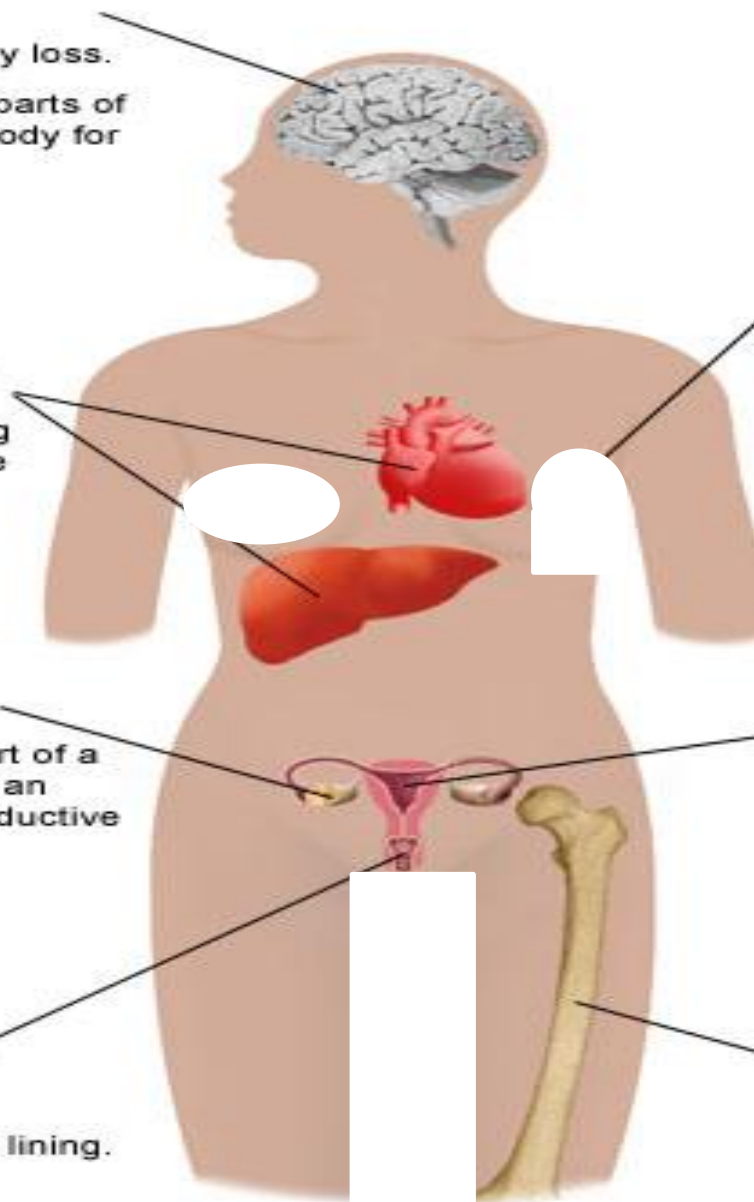
Uterus

Estrogen stimulates the maturation of the uterus.

Estrogen helps to prepare the uterus to nourish a developing fetus.

Bone

Estrogen helps to preserve bone density.



Adverse effects of estrogen

1. **Nausea and breast tenderness** (most common)
2. ***Postmenopausal* uterine bleeding**
3. **Thromboembolic** events, myocardial infarction
4. Breast and endometrial **cancer** [Note: The increased risk of endometrial cancer can be offset by including a progestin along with the estrogen therapy]



Breast Cancer



Thromboembolism



Myocardial infarction



Headache



Peripheral edema



Hypertension



Nausea

Some adverse effects associated with estrogen therapy

Progestins

- **Natural Progesterone:** not used widely as a therapy because of its rapid metabolism, resulting in low bioavailability
- **Synthetic Progestins:** more stable to first-pass metabolism, allowing lower doses when administered orally, these agents include:
 - ☐ *Norethindrone*
 - ☐ *Norgestimate*
 - ☐ *Drospirenone*
 - ☐ *Levonorgestrel*
 - ☐ *Medroxyprogesterone acetate*

Adverse effects of Progestin

1. Headache
2. Depression
3. Weight gain
4. Changes in libido

Headache



Depression



Weight gain



Changes in libido



Some adverse effects associated with progestin therapy